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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/617,978	07/11/2003	Rafael Herrmann	035718/260673	4095

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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	**PAPER NUMBER**
1638	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,978	HERRMANN ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,13-26,30,31,38,40 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,13-26,30,31,38,40 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *search results*.

DETAILED ACTION

1. The finality of the Office action mailed 26 May 2006 is withdrawn in light of the modified rejections below.

2. Claims 1-7, 13-19, 21-26, 30-31, 38, 40 and 42 are pending.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. On 4 Amy 2007 Applicant was offered claim amendments that would delete reference to pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14 in claims 1, 13 and 23. Applicants' representative, David Cash, refused.

Claim Rejections - 35 USC § 112

5. Claims 1-7, 13-19, 21-26, 30-31, 38, 40 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action mailed 26 May 2006, as applied to claims 1-7, 13-19, 21-27, 29-31, 38, 40 and 42. Applicant's arguments filed 8 January 2007 have been fully considered but they are not persuasive.

The claims are drawn to pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14.

Nucleic acids with 95% identity to the recited 177 bases of SEQ ID NO:17 or SEQ ID NO:14 would have 8 nucleotide substitutions relative to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14. These nucleic acids thus encompass those that encode proteins with 8 amino acid substitutions relative to the 58 amino acid long SEQ ID NO:20; these proteins would have 86% identity to SEQ ID NO:20.

The claimed nucleic acids encode proteins with any type of substitution, insertion or deletion relative to SEQ ID NO:20.

The specification does not describe the relevant characteristics or motifs of the claimed nucleic acids.

The claimed function of nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14 is that the encoded proteins be pesticidal. The pesticidal function is not specific; even the specification lists 4 pages of different pests (pg 50-53).

The structural features that distinguish pesticidal proteins with 86% identity to SEQ ID NO:20 from other proteins with 86% identity to SEQ ID NO:20 are not described in the specification. The structural features that associate structure with activity against a specific pest are not described. The necessary and sufficient structural elements of a protein with pesticidal activity are not described.

All of the claimed nucleic acids are novel, and thus the prior art cannot provide no well-developed field of prior art to describe the full scope of claimed nucleic acids. However, Zeng et al (2006, Peptides 27:1745-1754) teach that the four proteins most closely related to SEQ ID NO:20, are toxic or lethal to mice (pg 1749, left column).

The only species described in the specification are bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14, both of which encode SEQ ID NO:20.

Since the disclosure fails to describe the common attributes that identify members of the genus, and because the genus is highly variant, bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14 alone are insufficient to describe the claimed genus.

Hence, Applicant has not, in fact, described pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14. Because the sequences are not described, the method of using the sequences to alter a plant pest resistance is likewise not described, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the compositions used in the claimed methods, it is not clear that Applicant was in possession of the claimed genus at the time this application was filed.

Applicant urges that sequences that fall within the scope of the claims, guidance for making alterations, methods for assaying, guidance for determining percent identity and specific mutations that fall within the scope of the claims (Brief, pg 5).

This is not found persuasive. Zeng et al (2006, Peptides 27:1745-1754) teach that the four proteins most closely related to SEQ ID NO:20, are toxic or lethal to mice (pg 1749, left column). The structural features that distinguish pesticidal proteins with 86% identity to SEQ ID NO:20 from other proteins with 86% identity to SEQ ID NO:20 are not described in the specification.

Applicant urges that the Written Description Guidelines and *Lilly* state that written description requires a precise definition by structure, which is present in the 95% identity recitation (Brief, pg 5-7).

This is not found persuasive. *Enzo* states: "the written description requirement would be met ... if the functional characteristics of [a genus of polypeptides] were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed" (emphasis added). The correlation between that function and a structure is not sufficiently known in birtoxin-related proteins as a whole, and the description and assays provided in the specification are insufficient.

Only a portion of the structural features have been described - the percent identity to SEQ ID NO:14 or 17. But because this includes nucleic acids in which the protein sequence has a large number of amino acid substitutions, those amino acid substitutions that do not alter the function of the protein must be described. They are not.

Applicant urges that Example 14 of the Written Description Guidelines says that proteins with 95% identity to a given sequence identifier and that have a specified activity are described (Brief, pg7-8).

This is not found persuasive. The instant claims are not drawn to proteins with 95% identity to a given sequence identifier and that have a specified activity or to nucleic acids encoding such proteins. The claims encompass nucleic acids that encode proteins that have 86% identity to SEQ ID NO:20. Thus, the fact pattern in the instant case is different from that in Example 14 of the Written Description Guidelines.

Applicant urges that a description of a representative number of species does not require the description to be such that individual support of provided for each species (Brief, pg 8)

This is not found persuasive because the specification does not describe the sequence of even one nucleic acid encoding a pesticidal protein with 8 amino acid substitutions relative to SEQ ID NO:20. Thus, Applicant was not in possession of the full scope of the genus as claimed.

6. Claims 1-7, 13-19, 21-26, 30-31, 38, 40 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding proteins with 95% identity to SEQ ID NO:20, expression cassettes, host cells, and viruses comprising them, and methods of using them to alter plant pest resistance, does not reasonably provide enablement for pesticide-encoding nucleic acids with 95% identity to bases 73-249 of SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14, expression cassettes, host cells, viruses, plants and seeds comprising them, and methods of using them to alter plant pest resistance. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The rejection is modified from the rejection set forth in the Office action mailed 26 May 2006, as applied to claims 1-7, 13-19, 21-27, 29-31, 38, 40 and 42. Applicant's arguments filed 8 January 2007 have been fully considered but they are not persuasive.

The claims are broadly drawn to nucleic acids encoding pesticidal proteins with 95% identity to SEQ ID NO:20 and to pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14. The claims are also drawn to

expression cassettes, host cells, viruses, vectors, and plants comprising the nucleic acids, and methods of making the plants.

The instant specification, however, only provides guidance for isolation of proteins from arthropod venom and sequencing of the proteins (examples 1-4), southern corn rootworm and homopteran feeding assays (examples 5-6), construction of baculoviruses and expression of the proteins in insect cells (examples 7-8), construction of plant expression vectors encoding the pesticidal protein operably linked to a secretion signal sequence (examples 9-12), identification of cDNAs encoding neurotoxins from Centruroides vittatus and construction of vectors encoding them (examples 13-14); general guidance for transformation of rice, maize, soybean and assay of the plants for insect resistance (examples 15-20). SEQ ID NO:20 is Aam1 from Androctonus amoreuxi; SEQ ID NO:14 is a nucleic acid encoding it that uses rice-preferred codons and the sweet potato sporamin signal sequence, while SEQ IDNO:17 is optimized for expression in Stretomyces coelicolor and has the BAA signal peptide (paragraph spanning pg 11-12).

The instant specification fails to provide guidance for how to make pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14.

Nucleic acids with 95% identity to the recited 177 bases of SEQ ID NO:17 or SEQ ID NO:14 would have 8 nucleotide substitutions relative to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14. These nucleic acids thus encompass those that encode proteins with 8 amino acid substitutions relative to the 58 amino acid long SEQ ID NO:20; these proteins would have 86% identity to SEQ ID NO:20.

The guidance in the specification with respect to making amino acid substitutions in the proteins produced by the claimed nucleic acids is as follows:

The specification teaches making amino acid substitutions, deletions, truncations and insertions by methods including DNA shuffling and mutations, and suggests that conservative substitutions may be preferable, but are not required (pg 18, line 6, to pg 19, line 28).

Thus, from the guidance in the specification, it would appear that the vast majority of the amino acids in SEQ ID NO:20 could be substituted with any other amino acid.

SEQ ID NO:20 has 63-66% identity to four scorpion proteins, birtoxin, bestoxin, ikitoxin and dortoxin, taught by Hammock et al (WO 2003/028666, see search results), and these protisn have an even higher degree of relatedness if conservative amino acid substitutions are taken in account.

Zeng et al (2006, Peptides 27:1745-1754) teach that although the proteins have very similar structures, they have very different functions; birtoxin and dortoxin are lethal to mice, and bestoxin causes writhing in mice (pg 1749, left column).

SEQ ID NO:20 is much less related to other insect toxins of this protein class than to the mammalian toxins; for example, it only has 43-45% identity to four taught by Herrman et al (WO 2000/078957; see search results).

Thus, SEQ ID NO:20 may be a mammalian toxin, in which case, it would be unclear how one would use a plant transformed with a nucleic acid encoding it.

Further, even if SEQ ID NO:20 were not toxic to mammals, one of skill in the art would not know which 8 amino acid substitutions to make in SEQ ID NO:20 and still produce proteins

that are toxic to insects but not mammals, and the closest proteins to which to make comparisons are mammalian toxins.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:20 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain pesticidal but not mammalicidal activity of the encoded protein. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

Further, making each additional mutation in a protein has an negative effect on the success of the outcome. Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, making and analyzing proteins with 8 amino acid substitutions that also have pesticidal activity would require undue experimentation.

Thus, extensive teachings are required for making nucleic acids encoding pesticidal proteins with 8 amino acid substitutions relative to SEQ ID NO:20, as encompassed by the claimed nucleic acids. These teachings are not provided for by the specification. The specification also fails to overcome the unpredictability of making large numbers of amino acid substitutions in SEQ ID NO:20 as it provides no working examples of proteins with 8 amino acid substitutions relative to SEQ ID NO:20.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate

pesticide-encoding nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

Applicant urges that sequences that fall within the scope of the claims, guidance for making alterations, methods for assaying, guidance for determining percent identity and specific mutations that fall within the scope of the claims (Brief, pg 9-10).

This is not found persuasive because the guidance is insufficient, given the scope of the claims and the potential mammalian toxicity of the proteins. Limiting the percent identity of the claimed nucleic acid and requiring a function do not teach which amino acid substitutions may be made in the proteins. The guidance on pg 23-28 merely discusses fragment size, percent identity, and calculation of percent identity. However, guidance for determining percent identity does not teach which amino acid substitutions are permissible. The guidance fails to sufficiently teach which 8 amino acid substitutions to make in SEQ ID NO:20, given the unpredictability in making amino acid substitutions in birtoxin-related proteins.

Applicant urges that that the amount of experimentation required is not undue - the specification suggests shuffling, citing Minshull and Christians (Brief, pg 11)

This is not found persuasive. DNA shuffling requires another DNA or DNAs to do the shuffling with. Applicant does not teach which DNAs to use. Further, given the complex relationship between structure and function in birtoxin-related proteins (See Zeng et al, pg 1749, left column), it is not clear that proteins that are toxic to pests but not mammals can even be

made. Thus, making nucleic acids within the full scope of the claims requires undue experimentation. Minshull and Christians could not be considered because they were not sent.

Applicant urges that Lazar and Hill show that making protein substitutions and testing for activity was routine (Brief, pg 11)

This is not found persuasive because neither Lazar nor Hill made substitutions in 86% of the proteins they were working on, and neither were working on proteins whose closest relatives are mammalian toxins. Thus, one would need to randomly make nucleic acids encoding proteins with 8 amino acid substitutions and test them. Because the lack of guidance in the specification means this would require trail and error experimentation, because of the likelihood of protein inactivation (see Guo et al, pg 9209, right column, paragraph 2), this experimentation would be undue.

Applicant urges that the claims require that the proteins be pesticidal for Homopterans and Lepidopterans, and thus encompass only functional variants; guidance is provided on pg 18 and examples 5, 6 and 17 (Brief, pg 12)

This is not found persuasive. Pg 18 merely suggests that conservative substitutions may be preferable, but are not required. Given the instant proteins close relatedness to mammalian toxins, and the specification's lack of guidance as to which amino acids can be substituted and still retain pestical function without adding mammalian toxicity (if SEQ ID NO:20 isn't already a mammalian toxin), making the claimed nucleic acids would require undue experimentation. Assays, as provided in examples 5, 6 and 17, do not teach how to make the claimed nucleic acids.

Applicant urges that making all possible variants is not required; the specification tecahs how to make the claimed nucleic acids (Brief, pg 12-13)

This is not found persuasive because given the lack of guidance, one must practice trail and error experimentation to make the claimed nucleic acids, if nucleic acid that encode pesticidal, but not mammalicidal proteins, with 8 amino acid substitutions relative to SEQ ID NO:20 can even be made.

Applicant urges that the references cited support the position that the procedures needed to make the claimed nucleic acid are routine (Brief, pg 13-14) .

This is not found persuasive. Neither Lazar nor Hill made substitutions in 86% of the proteins they were working on, and none were working on proteins whose closest relatives are mammalian toxins. Thus, one would need to randomly make nucleic acids encoding proteins with 8 amino acid substitutions and test them. Because the lack of guidance in the specification means this would require trail and error experimentation, because of the likelihood of protein inactivation (see Guo et al, pg 9209, right column, paragraph 2) and converting the protein to a mammalian toxin, if it isn't already, this experimentation would be undue.

Applicant urges that Lazar is drawn to transforming growth factor alpha, a small mammalian peptide and Hill is drawn to ADP-glucose pyrophosphorylase; both proteins are unrelated to the instant proteins and thus irrelevant to the claims (Brief, pg 14-15)

However, Lazar et al and Hill et al teach the unpredictability in making amino acid substitutions in proteins, and this unpredictability is applicable to other proteins. Further, both Lazar et al and Hill et al only made single amino acid substitutions. The claims encompass nucleic acids that having 95% identity to SEQ ID NO:14 or 17 and encoding pesticidal proteins

with 8 amino acid substitutions relative to SEQ ID NO:20. Guo et al teaches that increasing the number of substitutions above single amino acid changes additively increases the probability that the protein will be inactivated (pg 9209, right column, paragraph 2). Thus, without further guidance, one of skill in the art could not make this many substitutions and still produce functional proteins.

7. Claims 1-7, 13-19, 21-26, 30-31, 38, 40 and 42 are free of the prior art, given the failure of the prior art to teach or suggest an isolated nucleic acid encoding SEQ ID NO:20 or nucleic acids with 95% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14. The closest prior art is that of Inceoglu et al (2001, Eur. J. Biochem. 268:5407-5413), who teach a nucleic acid that encodes a protein with 60% identity to SEQ ID NO:20, and Herrmann et al (WO200078957) who teach a nucleic acid with 61% identity to bases 73-249 or SEQ ID NO:17 or bases 64-240 of SEQ ID NO:14

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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Anne R. Kubelik, Ph.D.
May 9, 2007